Evaluation and Incorporation of Child/Adult Toxicokinetic Differences

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Science Questions

- Are there differences in toxicokinetics (TK) of xenobiotics between children and adults due to physiological changes and the immaturity of enzyme systems and clearance mechanisms?
- How could these differences be incorporated into physiologically-based pharmacokinetic models that simulate fate of environmental toxicants in both children and adults?

Research Goals

- Develop a children's PK database to compare standard PK parameters between children of different ages and adults. Parameters include: half-life, clearance, volume of distribution, AUC, and Cmax.
- Determine the size of adult/child PK differences. Evaluate whether children's differences are below 3.2x.
- Determine key differences between adults and children in metabolism and elimination pathways.

Background

Children's risks from environmental toxicant exposure can be modified by toxicokinetic factors that affect the internal dose of parent chemical or active metabolite(s). There are numerous physiologic differences between children and adults that affect toxicokineticincluding size of lipid, tissue compartments, blood flows, protein binding capacity, and immature function of hepatic and extrahepatic organ systems.

While there is very little TK data for environmental agents in children, there is a wealth of such data for therapeutic drugs used in pediatric practice. Using published literature, a children's PK database has been compiled by NCEA sponsored research which compares PK parameters between children and adults for 45 drugs. This has enabled comparison of child and adult PK function across a number of cytochrome P450 (CYP) pathways, as well as certain Phase II conjugation reactions and renal elimination. PK parameters for children are currently not factored into risk assessment process.

Methods/Approach

- Search published literature for child and adult PK data.
- Select drugs with the greatest amount of information on children's PK data. Table 1 shows chemicals in the database.
- Organize database by chemical, PK parameters, and age group. Tables 2 show database age groups and parameters.
- Categorize drugs by metabolism/clearance pathways based upon published literature sources (see Table 1).
- Analyze adult/child PK differences by regression analysis. Normalize adult parameters back to a single drug.
- Analyze inter-subject variability by probit plots and by plotting individual child data.
- Multiple Regression Analysis for the Means Database For Data Groups Within Each Parameter.
- Weighting options explored:
  1. *Equal weight for each data group*
  2. *Weight equal to square root of n (some imputations needed when n not given)*
  3. *Weight based upon variance in data (inverse of the square of ration of S.E. to mean; additional imputations needed when either n or standard deviation was not given.*
- Choice 3 proved to be best performing option.

Table 1

Chemicals (N=44) in Children's PK Database: Major Fate Pathways

CYP Pathways	Chemical	Non-CYP Pathways	Chemical
Cyp1A2	Bupivacaine	Alcohol dehydrogenase	Chloral hydrate
	Caffeine		Ethanol
	Mepivicaine		
	Theophylline	Glucuronidation	Lorazepam
			Morphine
			Oxazepam
Cyp2A6	Cotinine		Trichloroethanol
	Nicotine		Valproic Acid
			Zidovudine
Cyp2C9/ 2C19	Amobarbital	N-acetyltransferase	Dapsone
	Thiopentone		
	Tolbutamide	Sulphation/Glucuron.	Metoclopramide
			Paracetamol
Cyp3A or 3A4	Alfentanil	Renal	Ampicillin
	Carbamazepine		Cimetidine
	Fentanyl		Furosemide
	Lignocaine		Gentamicin
	Midazolam		Piperacillin
	Nifedipine		Ticarcillin
	Quinidine		Tobramycin
	Remifentanil		Vancomycin
	Teniposide		
	Triazolam	Biliary	Bromsulphalein
Multiple Cyp's	Antipyrene	Unclassified	Busulfan
	Dichloroacetate		Clavulanic Acid
			Ketamine

Table 2

Parameters, Chemicals and Subjects in the Mean Database

AUC	30	9	345
Clearance	87	26	2061
Cmax	15	5	173
T1/2	132	41	1764
Vd	70	25	882
Full database	334	44	5216

Results/Conclusions

These comparisons indicated that premature and full-term neonates tend to have 3 to 9 times longer half-life than adults for drugs included in the database. This difference disappears 2-6 months of age and beyond this age, half-life can be shorter than adults for specific drugs and pathways. These findings present a PK developmental profile that is relevant to environmental toxicants metabolized and cleared by the pathways represented in the database.

- **Children below 2 months have a 2-4 fold longer half-life and show greater variability (Figure 1)**
  - *25% of datapoints are outside the 3.2x adult variability range.*
  - *7% of datapoints are outside the 10x adult variability range.*
- **Beyond 6 months of age, a child's half-life for certain drugs can be shorter than an adults (Figure 2).**
- **The greatest child/adult PK differences occur before 2 months.**
  - *Addressing data gaps in this period of development is important for evaluating exposure and risks in children.*
- **Neonate/Adult PK differences need to be analyzed in relation to toxicity/PK mechanisms.**
  - *Parent compound toxicity: neonate may be more susceptible.*
  - *Metabolite toxicity: neonate may be less susceptible (unless clearance of metabolite highly impaired).*
- **Child/Adult PK differences can be incorporated into age-specific PBPK models.**
  - *Implications will be explored in case studies of environmental toxicants.*

Figure 1

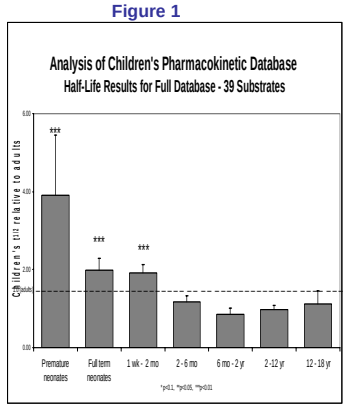
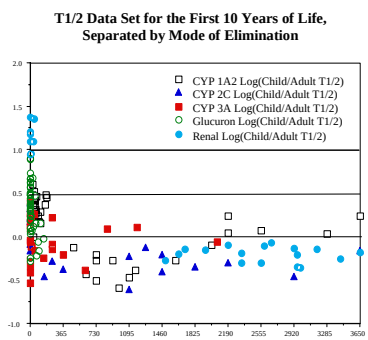


Figure 2



Impact and Outcomes

Chemical dosimetry will likely differ across children's developmental stages and in general between children and adults. Risk assessments can begin to describe the implications of these child/adult differences by appreciating how toxicokinetics can affect toxicant action and elimination, and by considering the functional status of these dynamic mechanisms in early life. PBTK models for environmental toxicants are needed for quantitative evaluation of dosimetry differences across age groups based on better understanding of physiological development and enzyme maturation processes. Application of such approaches will be critical in demonstrating whether the traditional uncertainty factors used in adult-based assessments are appropriate to account for sources of variability introduced by life-stages, species, route, and dose extrapolations.

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Susceptible Subpopulations

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